DEPARTMENT OF DEFENSE

MILITARILY CRITICAL TECHNOLOGIES LIST

SECTION 4: BIOMEDICAL TECHNOLOGY

April 2007

Under Secretary of Defense, Acquisition, Technology and Logistics
Pentagon, VA

PREFACE

A. THE MILITARILY CRITICAL TECHNOLOGIES PROGRAM (MCTP)

The MCTP supports the development and promulgation of the congressionally mandated Militarily Critical Technologies List (MCTL) and the Developing Science and Technologies List (DSTL).

Congress assigns the Secretary of Defense the responsibility of providing a list of militarily critical technologies (the MCTL) and of updating this list on an ongoing basis. The MCTL identifies technologies crucial to weapons development and has been a key element in evaluating U.S. and worldwide technological capabilities. The MCTP has provided the support for a wide range of assessments and judgments, along with technical justifications for devising U.S. and multilateral controls on exports. The DSTL, another MCTP product, identifies technologies that may enhance future military capabilities and provides an assessment of worldwide science and technology (S&T) capabilities.

The MCTP process is a continuous analytical and information-gathering process that refines information and updates existing documents to provide thorough and complete technical information. It covers the worldwide technology spectrum and provides a systematic, ongoing assessment and analysis of technologies and assigns values and parameters to these technologies.

Technology Working Groups (TWGs), which are part of this process, provide a reservoir of technical experts who can assist in time-sensitive and quick-response tasks. TWG chairpersons continuously screen technologies and nominate items to be added or removed from the list of militarily critical technologies. In general, TWG members are drawn from about 1,000 subject matter experts (SMEs) from the military Services, DoD and other federal agencies, industry, and academia. A balance is maintained between public officials and private-sector representatives. TWGs collect a core of intellectual knowledge and reference information on an array of technologies, and these data are used as a resource for projects and other assignments. Working within an informal structure, TWG members strive to produce precise and objective analyses across dissimilar and often disparate areas. Currently, the TWGs are organized to address 20 technology areas:

- Aeronautics
- Armament and Energetic Materials
- Biological
- Biomedical
- Chemical
- Directed Energy Systems
- Electronics
- Energy Systems
- Ground Combat Systems
- Information Security
- Information Systems
- Lasers, Optics, and Imaging
- Processing and Manufacturing
- Marine Systems
- Materials and Processes
- Nuclear Systems
- Positioning, Navigation, and Time
- Signature Control
- Space Systems
- Weapons Systems

B. THE MILITARILY CRITICAL TECHNOLOGIES LIST (MCTL)

The expanded MCTL provides a coordinated description of existing goods and technologies that DoD assesses would permit significant advances in the development, production, and use of military capabilities by potential adversaries. It includes goods and technologies that enable the development, production, and employment of weapons of mass destruction (WMD) and their means of delivery. It includes discrete parameters for systems; equipment; subassemblies; components; and critical materials; unique test, inspection, and production equipment; unique software, development, production, and use know-how; and worldwide technology capability assessments.

C. LEGAL BASIS FOR THE LIST OF MILITARILY CRITICAL TECHNOLOGIES

The Export Administration Act (EAA) of 1979 assigned responsibilities for export controls to protect technologies and weapons systems. It established the requirement for DoD to compile a list of militarily critical

technologies. The EAA and its provisions, as amended, were extended by Executive Orders and Presidential directives.

D. USES AND APPLICATIONS

The MCTL is not an export control list. Items in the MCTL may not appear on an export control list, and items on an export control list may not appear in the MCTL. The document is to be used as a reference for evaluating potential technology transfers and for reviewing technical reports and scientific papers for public release. Technical judgment must be used when applying the information. It should be used to determine if the proposed transaction would result in a transfer that would give potential adversaries access to technologies whose specific performance levels are at or above the characteristics identified as militarily critical. It should be used with other information to determine whether a transfer should be approved.

This is the first time that, MCTL Section 4: Biomedical Technology has been developed.

INTRODUCTION

A. ORGANIZATION OF THE MILITARILY CRITICAL TECHNOLOGIES LIST (MCTL)

The MCTL is a documented snapshot in time of the ongoing MCTP militarily critical technology process. It includes text and graphic displays of technical data on individual technology data sheets.

Each section contains subsections devoted to specific technology areas. The section front matter contains the following:

- *Scope* identifies the technology groups covered in the section. Each group is covered in a separate subsection.
- *Highlights* identify the key facts in the section.
- *Overview* discusses the technology groups identified under "Scope."
- *Background* provides additional information.

Each technology group identified under Scope has a subsection that contains the following:

- *Highlights* identify the key facts found in the subsection.
- *Overview* identifies and discusses technologies listed in data sheets that follow.
- *Background* provides additional information.
- *Data Sheets*, which are the heart of the MCTL, present data on individual militarily critical technologies. The principal data element is the Critical Technology Parameter, which is the technology parameter that defines where the technology would permit significant advances in the development, production and use of military capabilities of potential adversaries.

B. TECHNOLOGY DATA SHEETS

The technology data sheets are of primary interest to all users. They contain the detailed parametric information that managers, R&D personnel, program managers (PMs), and operators need to execute their responsibilities.

- *Critical Technology Parameter(s)* includes the parameter, data argument, value, or level of the technology which would permit significant advances in the development, production and use of military capabilities of potential adversaries.
- *Critical Materials* are those materials that are unique or enable the capability or function of the technology.
- *Unique Test, Production and Inspection Equipment* includes that type of equipment that is critical or unique.
- *Unique Software* is software needed to produce, operate, or maintain this technology that is unique.
- *Major Commercial Applications* addresses commercial uses of this technology.
- *Affordability Issues* are those factors that make this technology an affordability issue.
- *Export Control References* indicate international and U.S. control lists where this technology is controlled.

  Note: Export control references are:

WA ML 2	(Wassenaar Arrangement Munitions List Item)
WA Cat 1C	(Wassenaar Dual Use List Subcategory)
MTCR 17	(Missile Technology Control Regime Item)
NTL B3	(Nuclear Trigger List Subitem – Nuclear Suppliers Group)
NDUL 1	(Nuclear Dual Use List Item – Nuclear Suppliers Group)
AG List	(Australia Group List)
BWC	(Biological Weapons Convention)
CWC	(Chemical Weapons Convention)

USML XII	(United States Munitions List Category – ITAR)
CCL Cat 2B	(Commerce Control List Subcategory – EAR)
NRC A	(Nuclear Regulatory Commission Item)

- *Background* provides a description of the technology.

SECTION 4—BIOMEDICAL TECHNOLOGY

Scope

Highlights

- Current research reveals elements of human and animal genome that increase susceptibility to disease.
- Genetically engineered agents comprised of moderate pathogens and selected animal or human immune response modifiers can generate severe or fatal illness.
- Genomic sequences in animals and humans coding for polymorphisms in specific neurotransmitter related enzymes or in neurotrophic factors have been associated with working memory or with inducing increased anxiety during stress. The large scale introduction of such genes through a viral vector, into combat forces or decision makers will markedly reduce U.S. combat capability.

OVERVIEW

The expression of clinical symptoms in a patient population exposed to biological threat agents is a function both of the nature and dosage of the threat agent as well as of the response of the host (human, animal, plant) to the agent. The Biotechnology portion of this MCTL (Part 3) is concerned with the nature and militarization of the threat agent, mechanisms of production and dispersion of the agent and group and individual protection related to that threat agent. This Biomedical Section (Section 4) addresses those technologies or materials that will degrade a soldiers performance or increase a soldiers susceptibility to disease; also included may be those technologies or materials that enhance a soldiers vigilance, stamina, alertness or resistance to CBW agents. The response of the soldiers to materials that will enhance or degrade performance and susceptibility is related to their wellness and nutritional status and the presence of specific host genes that may increase susceptibility or resistance of the host. The availability of sensing systems that measure the response of the host to vigilance enhancing materials or to infectious agents will enable prediction of which exposed persons will experience degraded performance or become ill. It is known that individuals that are infected with parasites may be more susceptible to infectious agents than persons who are in a good state of health. It has been shown that exposure of rodents to a mild pathogen may develop catastrophic disease if the pathogen has a normally occurring immune response modifier gene from the host incorporated into the agent genome. In addition to the increased virulence of the bioagent, such genetic modifications also generate a clinical disease that is much more difficult to manage because the immune competence of the infected person is compromised.

The majority of the items included in this section of the MCTL relate to genomic sequences of the host that predispose an individual to disease or to loss of attentiveness and in this sense the militarily critical information is in the know-how related to coding of the genome rather than in equipment or material products. Such information resides within hosts and may be discovered by persons skilled in the art of genomic sequencing. The open literature in 2006 contains some information identifying human and rodent genomic sequences that may predispose an individual to specific illness including infectious disease or to changes in abilities related to working memory and to increased susceptibility to anxiety in stressful situations. Since the decoding of the human and other animal genomes is still at an emergent state at this time, the likelihood is very high that many more human biomarkers of susceptibility will be discovered in the coming decade. The broad distribution of information concerning which host genes, when incorporated into the genome of potential pathogens, will give rise to very potent biological agents are likely to present a major threat to our military forces and civilian population. This is because the costs associated with identifying, by molecular and clinical research, those host genes that confer resistance or susceptibility to infection are high (hundreds of millions if dollars) and this costs limits the capability of threat nations or non-state entities to develop biological agents based on host susceptibility. The rapid publication of such genomic information however lowers the economic barrier to acquisition of potentially critical military information thereby enabling development of a viable threat.

The biomedical technologies that are indicated by the blue shading are addressed in Section 4 (see Fig. 4.0-1). Figure 4.0-1 diagrams a three-dimensional volume having axes of direct military utility (Y axis), non-military utility (X axis) and availability of countermeasures (Z axis). The technologies embodied in the biomedical technology section are dual use technologies. It includes those technologies that have a dominant utility for military operations that may compromise markedly combat capability of the soldier.

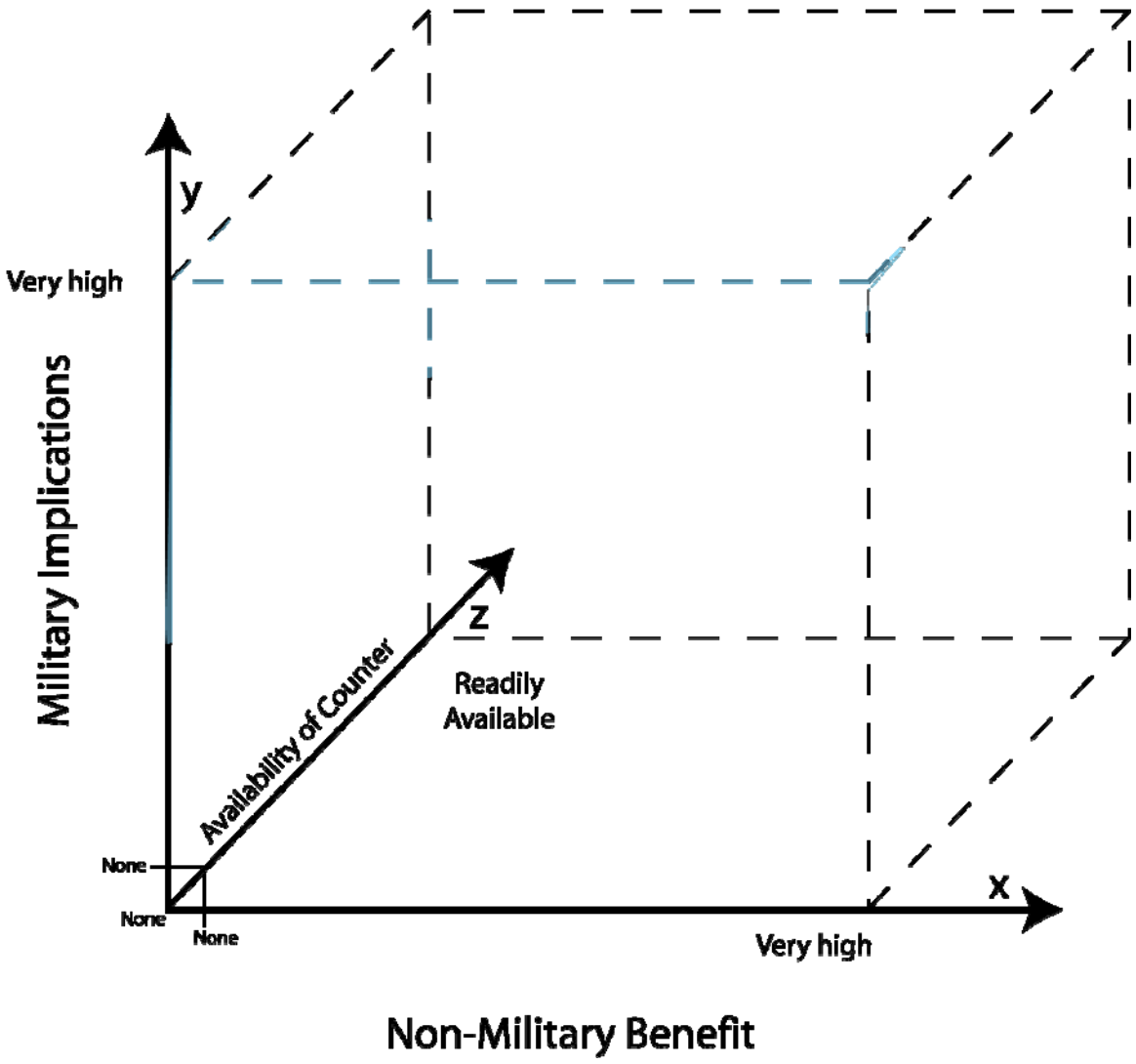

Figure 4.0-1. Military Implications and Non-Military Applications

The financial resources needed to perform genetic engineering are relatively small (< $100,000) if the specific genomic sequences required to enhance pathogenicity or circumvent host defense mechanisms are readily made available to threat nations and non-state groups.

BACKGROUND

During the past decade an international effort has been mounted to define the genetic code specifying all aspects of inheritable material that influences growth, development and structure of humans as well as the inheritable factors that predispose each person to illness or modified performance under stress. At the same time the genetic code defining infectious agents and selected species have also been analyzed and reported in the literature. The funding in this effort has been in the billions of dollars and in 2005 the genome of the human was by and large completed. During the next decade, the particular genes that predispose humans to or protect from diseases will be

identified as will those genes that confer susceptibility to or resistance to intense stress. Early reports indicate that genetic elements in the human can increase susceptibility to infectious disease and to stress. When some of the infectious agents are modified with a particular set of human or mammalian genes that code for immunosuppressive molecules, the threat potential of the infectious agents can become much greater. Alternatively it is possible to engineer a non-pathogenic or a commensal organism containing immune or stress-response modifiers to compromise a population's immune response. A subsequent release of a relatively benign agent would then cause catastrophic results. Genomic sequences that code for particular catechol-O-methyl transferase polymorphisms have been shown to be associated with human abilities related to working memory (working memory is essential for coherent decision making). Genomic sequences that code for brain derived neurotrophic factor polymorphisms have been associated with elevated anxiety in stressful situation. The ability to intentionally increase anxiety in deployed forces may be expected to have a profound effect on operational capability.

SECTION 4.1—HOST GENOME RELATED TO DISEASE

Highlights

- Human and animal genes that regulate host immune responses to microorganisms and viruses may be inserted into the genome of minimally or non-pathogenic microorganisms to create highly virulent agents.
- A fully infectious agent, poliovirus, has been synthesized de novo in the laboratory demonstrating that knowledge of a genomic sequence for creating an infectious agent from a non-pathogen can be rapidly translated into production of a desired newly created pathogen in a laboratory at minimal cost.

OVERVIEW

The international Human Genome Project has defined an initial set of genes in host animals, including humans, livestock and agriculturally useful plants that affect the susceptibility of these living organisms to naturally occurring emergent disease or to threats disseminated by adversaries. Related research has also defined which host cell genes, when inserted into the genome of threat organisms, could increase pathogenicity of the agent. Section 3 of the MCTL discusses the nature of infectious or toxic properties of agents identified by the Australia Group. This section addresses the properties of the host that facilitate infection, toxicity or disease resistance.

BACKGROUND

Susceptibility of a soldier to a pathogen is a function of the nutrition, neuropsychopharmacological characteristics, fitness and the genome of the person. Malnutrition increases susceptibility to infectious agents as does concurrent infections with parasitic organisms or persistent stress. The identification of important enzymes/gene products in the human, relevant to protection from Biological or Chemical induced injury, can be utilized in defense strategies. Relatively minor modifications in the nucleotide sequence of the gene coding for the major histocompatibility complex (a critical protein in humans and other mammals) markedly increases the susceptibility of the animal to viral infection by cytomegalovirus. Minor structural changes in another host cell gene Nramp1, results in marked susceptibility of the host to mycobacterial infection. [A Tuite and P Gros Microbes and Infection 8: 1647-1653 (2006)]. It is anticipated that many more such host genes affecting resistance or susceptibility to infectious disease will be identified in the coming years. The rapid genotyping of individuals is possible through the use of kits or chips that allow for genotyping for biomarkers of disease or chemical susceptibility. This has to be done only once in an individual's lifetime unless new relevant genes are identified. The genotyping of individuals, along with a catalogue of the manifestations of the various gene products alone, and in combination, could lead to more appropriate (and potentially reduced risk) job assignments. It will also allow intervention/protection strategies to be tailored to the individual, rather than the traditional one-size-fits-all approach. The genome of the host may also be involved in clinical development of infectious disease. In some cases genetic mutations that have a beneficial effect of protecting individuals from infectious diseases may have a deleterious consequence of compromising the function of that individual under stressful conditions. An example of this effect is the observation that individuals living in regions of the world with high incidence of malaria have an increased incidence of mutations in hemoglobin that confer resistance to malaria but also predispose the homozygous individual to sickle cell anemia with serious clinical consequences under conditions of reduced oxygen tension.

LIST OF MCTL TECHNOLOGY DATA SHEETS
4.1. HOST GENOME RELATED TO DISEASE

MCTL DATA SHEET 4.1-1. HUMAN GENES AFFECTING HOST IMMUNE RESPONSES

Genomic sequences of humans and livestock that inhibit the immune response of the host to potential pathogens in the environment.

Critical Technology Parameter(s)	Naturally occurring genomic sequences from humans and commercially important livestock that code for enhanced or diminished immune response of a host to naturally occurring minimally infectious agents. Portions of these host genomic sequences, when incorporated into a minimally or non-pathogenic organism, can generate virulent agents. The knowledge of the sequence of specific host genes (from humans or animals) that can convert non- or minimally pathogenic organisms into virulent agents is the critical technology parameter.
Critical Materials	Genomic materials that can diminish host immune responses include interleukins 4, 5, 10, 13, C Reactive Protein. Several molecular markers of the human lymphocyte also can diminish immune response. Conversely several immune modifiers markedly enhance immune response. These include Interleukin 2, interleukin 12, interferons alpha, beta and gamma.
Unique Test, Production, Inspection Equipment	Complete containment facilities at P3 or P4 level (BL3 or BL4) level with ability to grow pathogenic microorganisms, viruses or toxins without propagation of aerosols; centrifugal separators for pathogens or toxins without aerosol propagation and with one or more sealing joints in steam containment areas; polished internal stainless steel or titanium surfaces for in situ sterilization in a closed state. Production equipment that involves negative pressure in compartments involved in cell growth is of concern.
Unique Software	The identification of the polynucleotide sequence of the human genomic material, that when spliced into the minimally pathogenic agent, will confer marked increases in virulence and pathogenicity.
Major Commercial Applications	Production of chemotherapeutic agents useful in treating cancer, autoimmune disease.
Affordability	The cost of synthesizing polynucleotides (fragments of human genes) having a length of 300 bases is less than $20,000. The cost for acquisition of most naturally occurring biological agents is minimal.
Export Control References	Not controlled

BACKGROUND

The decoding of the human genome over the past decade has resulted in the identification of human genes that, when inserted into non-pathogenic viral particles, can markedly increase the susceptibility of persons exposed to such particles to virulent disease, to loss of cognitive function and to increase in anxiety. The virulent disease is caused by loss of immune competence rather than by exposure to a highly infectious agent of the Australia group. The loss of immune competence is similar to that seen in patients with acquired immunodeficiency syndrome (AIDS) or in transplant patients who are immuno-suppressed. The reduction in cognitive awareness is a result in perturbations in the expression of enzymes that regulate neurotransmitter levels.

.

SECTION 4.2—SENSORS FOR DETECTION OF EMERGENT DISEASE

Highlights

- Sensors for host genome analyses are based upon genomic or proteomic analyses. Because the genome of a person is constant only one analysis of the individual is required over the person's lifetime.
- The same equipment and material identified in MCTL Section 3 for sensing and identifying threat agents are applicable here. All the relevant sensors for human genome analyses are point detectors.
- Sample acquisition requires obtaining blood and subsequent separation of white blood cells.
- Different families of host genes are associated with susceptibility to biological agents.

OVERVIEW

The discussion of sensor systems presented in MCTL Section 3 is directly applicable to sensor systems use for characterizing host cell genetic factors or proteins associated with susceptibility or resistance to infectious disease. The total number of host genes that regulate resistance or susceptibility to disease is unknown at this time but it is a subset of the total set of the approximately 30,000 human host genes.

BACKGROUND

Genomic sequences that affect immunological function, behavior and/or metabolism can be introduced into humans and livestock by insertion of the desired sequence into a non-pathogenic viral vector. Appropriate delivery of the modified viral vector into a person can result in modified immune responses, behavior and metabolism in the exposed individual. Sensors can be constructed that will detect and identify the presence of an entire gene sequence or of a portion of the gene inserted into a viral vector.

Databases that provide information on the distribution of host genes that confer susceptibility to or resistance from disease can be integrated into the sensor and communication system to allow early assessment of force readiness and management actions needed to neutralize the impact of the attack. This approach utilizes both technical and public health approaches to manage the threat.

Gene probes provide the greatest capability of analyzing host samples that may indicate exposure to immuno-suppressor genes or behavior modifying genes. The genomic probes will react with nucleic acid sequences of genes inserted into viral vectors. As new disease susceptibility or resistance genes are identified, sensors can be modified to detect the occurrence of the genes in soldier samples.

The nucleic acid components can be detected using synthetic complementary DNA/RNA probes consisting of oligomers (20-25 nucleotides long) that were constructed to bind specifically to the host gene of interest. The probes can be immobilized on flat platforms (e.g., Affymetrix system) or on bead systems (e.g., Luminex xMAP system). Most often the oligomer probes are designed to react with amplicons produced from the sample of interest by PCR amplification. The amplification system requires release of the nucleic acid from host cells and subsequent iterative cycling with an enzyme system; this requires about 20 minutes to 60 minutes).

LIST OF MCTL TECHNOLOGY DATA SHEETS
4.2. SENSORS FOR DETECTION OF EMERGENT DISEASE

MCTL DATA SHEET 4.2-1. SENSOR SYSTEMS TO DETECT HUMAN GENOMIC SEQUENCES

Sensor Systems that use biological or biomimetic materials to detect human or livestock genomic sequences that have been incorporated into non-pathogenic viral delivery systems.

Critical Technology Parameter(s)	Capability of detecting and identifying a genomic sequence of a host immune response modifier that has been spliced into the genome of a non-pathogenic virus or bacterium or of a commensal organism. The sensor must be capable of detecting both the polynucleotide sequence of the human or livestock genome and the viral delivery vehicle at concentrations of agent that are sufficient to cause human dysfunction.
Critical Materials	Selected gene probes that bind non-pathogenic viral vectors containing portions of the genes for human immune response modifiers. The probes must detect and identify the modified vector with low rates of false positives and negatives.
Unique Test, Production, Inspection Equipment	High affinity antibodies for the host immune response modifier molecules produced in sufficient quantities (grams) and having reproducible binding properties for the response modifiers. Usually requires production of entire antibodies or Fa.b fragments in microorganisms such as E coli. Genomic based probes comprised of polynucleotide sequences (length 22–24 nucleotides) that can detect human genomic sequences affecting immune competence. Equipment for producing array chips/tickets.
Unique Software	Knowledge of the polynucleotide sequence of the human genomic material, that when spliced into the viral or bacterial delivery particle, will compromise immune competence of persons exposed to the delivery agent. Knowledge of the polypeptide products that can be generated in a host and, when expressed, will inhibit normal immune competence of the host.
Major Commercial Applications	Medical diagnostics, homeland security and civilian emergency response. Potential medical/pharmacological treatments for autoimmune disease and cancer.
Affordability Issues	Depends on the number of immune system modifiers that will be detected on a single platform. Some antibody based chips are capable of multiple reuses, test for 1–4 organisms range from $25–75. The genomic based systems with an array of detection spots for multiple organisms range from modest ($20–50) to expensive (several hundred dollars) for the most detailed and specific platforms. Reading equipment may cost $200 K.
Export Control References	Not controlled

BACKGROUND

Sensor systems can be developed that detect human genomic sequences.